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Review

Current status and advances in management of early breast cancer

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ABSTRACT

Breast cancer is the most common female cancer. Worldwide, more than a million women are diagnosed every year. However despite this increase, the mortality rate is declining. This is due to combination of factors including early diagnosis and effective treatment. This manuscript which is presented in two sections outlines the current status in management of early breast cancer. Section 1 focuses on the advances in diagnosis and surgical treatment of breast cancer and give an overview of the histopathological aspects. The focus of section 2 is on advances on adjuvant treatment of breast cancer including radiotherapy, chemotherapy and endocrine treatment.

1. Introduction

Breast cancer is the most common female cancer. Worldwide, more than a million women are diagnosed every year. In 2005 more than 45,500 women were diagnosed in the UK with breast cancer. In the last ten years, female breast cancer incidence rate in the UK have increased by 13%, however despite this increase, the mortality rate is declining (Fig. 1). There were 12,082 deaths from breast cancer; 11,990 (99%) of these were in women and 92 (1%) were in men.[1–3]

Multidisciplinary team (MDT) approach in management of breast cancer patients, joint clinics and weekly MDT meetings for diagnosis and treatment planning, remain central to the management and is regarded as one of the major advances in this field. It has led to tailoring therapy to the individual patients' needs with the involvement of all members of the team.

2. Breast cancer diagnosis

Diagnosis of breast cancer is carried out by triple assessment which includes clinical evaluation, breast imaging and tissue diagnosis (cytological or histological assessment).

Full-field digital mammography has allowed more confident identification and characterisation of microcalcifications, particularly in dense breast tissue. Digital equipment, although more expensive than analogue units, provides a major advantage in stereotactic procedures for impalpable lesions including guide wire placement, core biopsy and vacuum-assisted excision where small lesions can be completely removed percutaneously using a mammotome. Advances in the sensitivity of breast imaging and the extension of mammographic screening programmes in Europe and North America have undoubtedly contributed to the reported rising incidence of breast cancer, and the current controversy surrounding overdiagnosis of clinically unimportant lesions with potentially harmful overtreatment in some women.[4]

Breast magnetic resonance imaging (MRI) has become a widely-used second-line imaging modality with well-defined roles in assessing tumour multifocality and planning surgery[5] and in

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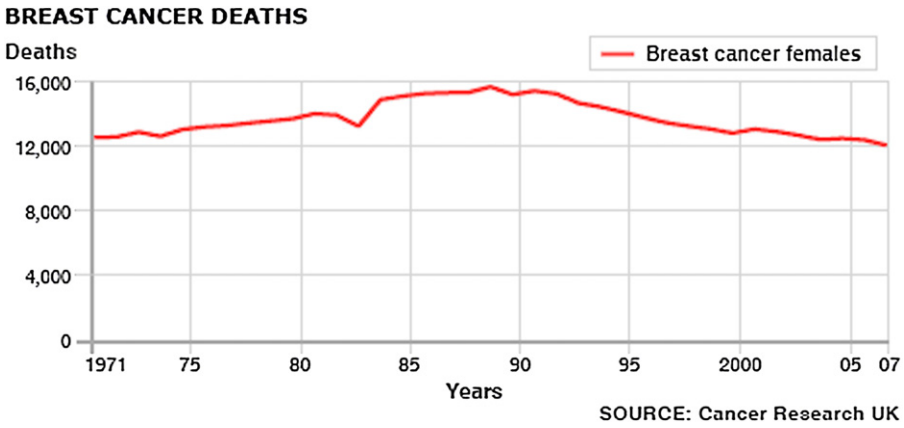

Fig. 1. Declining breast cancer mortality in the UK. (http://info.cancerresearchuk.org/cancerstats/types/breast/mortality/).

monitoring local tumour response to neoadjuvant chemotherapy. MRI screening is advised in high-risk young women such as those with a BRCA gene mutation or with previous mantle irradiation for lymphoma, and in assessing gel implants for leak or rupture.

3. Advances in surgical treatment

Over the last 30 years the major change in the surgical treatment of early breast cancer has been the shift towards breast conservation treatment. Breast conserving surgery (BCS) was introduced to reduce the physical and psychological consequences of removing the whole breast. Trials performed in the 1970s demonstrated equivalent survival when comparing BCS and radiotherapy with mastectomy.[6] Local recurrence rates were higher in the BCS and radiotherapy group. However patients developing local recurrence were salvaged by a mastectomy. Radiotherapy is now accepted as standard treatment for patients with early breast cancer undergoing BCS.

The meta-analysis conducted by the Early Breast Cancer Trialist's Collaborative Group comparing BCS with BCS and radiotherapy demonstrated that the addition of radiotherapy reduced the risk of local recurrence by 75% and resulted in a disease free survival advantage, with a decrease in the 15 year risk of dying of breast cancer from 31% to 26% in node negative patients and 55–48% in node positive patients.[7,8]

Between 1980 and 2004, the mastectomy rate at the Mayo Clinic fell from 91% to 36%.[9] Currently in the UK about two-thirds of newly diagnosed cancers are amenable to breast conservation (wide local excision and radiotherapy) but in the remaining third, mastectomy is still undertaken because of tumour size, location within the central breast, tumour multicentricity, or patient preference.

For patients undergoing breast conservation, breast surgeons trained in newer oncoplastic procedures can achieve better outcomes with regard to long-term cosmesis. Glanduloplasty techniques using local breast tissue flaps reduce the cavity left in the tumour bed and allow wide tissue margins around the tumour to be resected so that cancer clearance is not compromised.

In patients with large breasts, therapeutic mammoplasty can achieve better cosmetic outcomes and maintain breast symmetry. Here the tumour and surrounding margins are excised widely as part of a reduction mammoplasty, with the design of the nipple-areolar pedicle tailored to the area of tumour excision. Contra lateral breast reduction can be undertaken at the same time or at a later date. For the surgical team there is inevitably a considerable increase in requirements for operating theatre time with more complex oncoplastic surgery.

BCS aims to achieve good local control of both the primary tumour and regional nodes, and attention to histological clearance of margins is essential to ensure complete tumour excision. Local recurrence rates following BCS are the prime quality indicator for adequacy of surgery and the recommended minimum standard, and targets for local recurrence after BCS have now been revised to a maximum of 5% at 5 years and a target of <3% at 5 years.[10]

4. Advances in mastectomy and breast reconstruction

The technique of mastectomy has evolved steadily over the last 50 years with abandonment of the radical Halsted mastectomy in favour, initially of a modified procedure sparing the pectoral muscles, and more recently adopting skin-sparing techniques, where only the skin of the nipple–areola complex is included in the resection, to allow the uninvolved skin envelope to be conserved for breast reconstruction. Endoscopic breast surgery is an emerging technique which aims to reduce still further the extent of scarring on the breast, and is currently being undertaken in the context of clinical trials.[11]

UK and European guidelines for breast cancer treatment recommend that reconstruction should be available to women requiring mastectomy.[5] Immediate reconstruction can make the prospect of mastectomy easier to bear in some women, but not all patients will be suitable for immediate reconstruction. Some women may decline because of personal preference[12] and some women will be advised against immediate reconstruction for oncological reasons. The expanded indications for post-mastectomy radiotherapy (see Section 2 of this paper) has resulted in a move away from immediate reconstruction in patients with large or high-grade tumours or where lymphovascular invasion or nodal involvement predict the likely recommendation of chest wall radiation.

The concerns previously raised on the use of silicone gel implants have largely been dispelled[13] and implants are considered safe and effective components of the reconstructive armamentarium. Advances in gel cross-linking have reduced silicone “bleed” and cohesive gel implants are likely to experience fewer problems with late extracapsular rupture. Myocutaneous flaps using the latissimus dorsi (LD) muscle from the back or lower abdominal tissue based on the deep inferior epigastric perforators (DIEP flap) can replace relatively large volumes of breast tissue, either alone or in combination with implants, and are used both for immediate and delayed reconstruction. The LD flap is a robust reconstructive technique and is within the current training repertoire of most breast surgeons. The free DIEP flap technique requires

microvascular surgical expertise and usually takes 5–6 h of operating theatre time and is usually undertaken by the plastic surgical team.

5. Risk-reducing breast surgery

Risk-reducing (prophylactic) mastectomy and reconstruction is available for women at very high-risk, such as patients with previous breast cancer or women carrying a BRCA gene mutation.[14] Counselling and psychological assessment of women with an increased genetic predisposition is mandatory and the availability of immediate reconstruction is particularly important to the mental health of this group of patients and is the preferred option.[15]

Currently the most frequent clinical setting for risk-reducing mastectomy is in the contra lateral breast following unilateral breast cancer diagnosis. Young women in particular with a breast cancer diagnosis are increasingly opting for risk-reducing contra lateral mastectomy, both with invasive disease and in situ carcinoma, with reported increases from 2.1% to 5.2% overall (i.e. including patients suitable for breast conservation) and from 6.4% to 18.4% in those requiring mastectomy for treatment.[16]

6. Advances in regional nodal staging

Despite advances in genetic subtyping of tumours and increasingly sophisticated receptor analysis in breast cancers, the axillary lymph node status remains the strongest predictor of long-term prognosis in invasive disease.[17] Sentinel lymph node biopsy (SLNB) rather than full nodal clearance is accepted as the standard of care for axillary staging in early breast cancer, delivering less morbidity in terms of shoulder stiffness and risk of lymphoedema and offering a significantly reduced hospital stay.[17–22] Some centres are now offering upfront SLNB under local anaesthesia a week prior to definitive breast cancer surgery[23] however intra-operative diagnosis of sentinel lymph node is the way forward.[24]

Quality assurance and training of surgeons, pathologists and nuclear medicine physicians has been undertaken in breast units across the UK[25] and techniques have been standardised to ensure that SLNB avoids the pitfall of understaging axillary involvement (false negative SLNB) with consequent undertreatment. The double-dye localization technique, incorporating both radionuclide and Patent V blue dye injection, is regarded as superior to single-dye techniques. Frozen section reporting and imprint cytology of SLNB are used in some centres to enable further axillary surgery, where indicated, to proceed under the same anaesthetic. Currently trials are in progress to assess whether SLNB analysis with gene amplification can replace conventional histopathology.[26] The aim is to determine whether reliable and rapid intra-operative diagnosis can avoid readmission and second operations in patients with positive SLNB.[26] Currently there is controversy about the significance of detection of isolated tumour cells within the sentinel lymph node. With advances in gene analysis and profiling there may be no need for nodal surgery for staging purposes in future.

7. Histopathology of breast cancer

All breast cancers are adenocarcinomas arising from the terminal duct lobular units. Breast cancers are divided into two main categories, non invasive and invasive. Infiltrating ductal carcinoma is the most common breast cancer histology, accounting for about 80% of all breast cancers. Lobular carcinoma constitutes 10% of the breast cancers.

8. Non invasive breast cancer

Ductal carcinoma in situ (DCIS) is the most common type of non invasive breast cancer, accounting for about 15% of all newly diagnosed breast cancer cases. DCIS refers to an uncontrolled proliferation of cells that are confined to the breast duct so the basement membrane of the breast dusts remains intact. Eventually, the cells outstrip their blood supply and become necrotic centrally. This debris can calcify and be detected mammographically. DCIS is classified into five histological subtypes associated with varying prognostic implications. Recognized patterns include: solid, papillary, cribriform, micropapillary and comedo. Most lesions represent a combination of at least two of these subtypes. Comedo carcinoma is considered high-grade and predictive of recurrence. In patients with DCIS the invasive cancer usually occurs within the same breast, however women with DCIS are also at a higher risk of developing cancer in the contra lateral breast.[27]

Lobular carcinoma in situ (LCIS) is characterized as a benign-appearing proliferation of terminal ducts and ductules that is often multifocal and bilateral. LCIS is much less common and is associated with less risk of the development of invasive cancer than DCIS. LCIS is considered a marker that identifies women at increased risk of invasive breast cancer; it is typically multifocal and is frequently bilateral.

9. Invasive breast cancer

Invasive ductal carcinoma (IDC) is the most common type of breast cancer. About 80% of invasive breast cancers are classified as invasive ductal carcinoma. The tumour cells have penetrated the ductal basement membrane and infiltrates into the surrounding breast tissue. The invasive tumour is characterized by tumour cells arranged in cords, islands, and glands embedded in a dense fibrous stroma. The tumour cells have the potential to metastasize to other parts of the body through the bloodstream or lymphatic system. Most IDC's have no specific histological characteristics and are classified as No Special Type (NST).[27,28]

Invasive lobular carcinoma (ILC) originates in the lobules where it extends into the surrounding breast parenchyma. It is less common than IDC, accounting for about 10% of invasive breast cancers and has a tendency to be multifocal. Tumour cells are often arranged in single files/strands, but at times it may be difficult to distinguish from ductal carcinomas. Immunohistochemistry staining for E-Cadherin is helpful in differentiating ILC from IDC, ILC loses E-cadherin expression.[27]

9.1. Other histological types of breast cancer

Tubular carcinoma is a highly differentiated invasive carcinoma with limited metastatic potential and better than average prognosis. Medullary carcinoma is a relatively uncommon type of Invasive carcinoma, accounting for less than 5–7% of all invasive breast cancers. Mucinous carcinoma is an invasive form of breast cancer characterized by large amounts of extracellular mucin production and is associated with a relatively favorable prognosis. Invasive cribriform carcinoma is a well-differentiated cancer which shares some features with tubular carcinoma and is also associated with better than average prognosis. Adenoid cystic carcinomas similarly rarely spread to the lymph nodes or distant areas, and have a very good prognosis.

Pagets disease is a subtype in which malignant ductal cells extend intraepithelially into the epidermis of the nipple. The Paget cells, characteristic large cells surrounded by a clear halo-like area, invade the epidermis; underlying ductal carcinoma is almost always present. It accounts for approximately 1% of all breast

cancers. Invasive papillary carcinoma is very rare, comprising less than 1–2% of invasive breast cancers. Invasive micropapillary carcinoma is a distinct but poorly recognized variant with an incidence of less than 3% but is associated with a relatively poor prognosis with frequent skin invasion and extensive nodal involvement.

Inflammatory breast cancer is relatively rare, representing about 1–5% of all breast cancers. Lymphatic involvement of skin by underlying carcinoma, causing red, swollen, hot skin resembling an inflammatory process; peau d'orange and is associated with poor prognosis.

10. Basal type breast cancer

Basal type breast cancer was first described in 2003. The breast cancer cells have particular genetic changes. The p53 gene is damaged (mutated) or lost. The cells make large amounts of a protein called cytokeratin 5/6. Basal type breast cancers are often triple negative– meaning that they don't have many receptors for oestrogen, progesterone or Herceptin (HER). BRCA1/2-related breast cancers are more likely than non-BRCA1/2-related breast cancer to express a basal epithelial phenotype.[29,30]

11. Receptors

In current clinical practice, Oestrogen (ER), Progesterone (PR) and Her 2 testing is mandatory in all newly diagnosed breast cancers, and accurate results are critical in determining the use of adjuvant hormonal therapy. Immunohistochemistry is the method of choice to detect the nuclear steroid receptors in tumour cells and the membrane staining for HER2. Approximately 75% of breast cancers are hormone receptor positive and 15–25% are HER2 positive. The Hormone receptors are assessed using the Allred or Quick score where numerical scores are given to the percentage of nuclei containing the hormone and the intensity of staining up to a maximum of 8.

HER2 score is dependent on the percentage of cells staining and the intensity and completeness of membrane staining. A score of 3+ is deemed positive and patients qualify for Herceptin treatment. A score of 2+ is borderline and the tumour must be tested for gene amplification using Fluorescent in situ Hybridization (FISH). Around 15–20% of all breast cancers do not have hormone or HER2 receptors. Sometimes referred to as 'triple negative' breast cancer, these are typically more aggressive and difficult to treat. Breast cancer cells that overexpress HER2 are thought to have four to five time as many cancer stem cells compared with HER2 negative breast cancer cells.[31,32]

12. Adjuvant treatment of breast cancer

In addition to surgery, there are other treatment modalities for the management of breast cancer patients. These include radiotherapy, chemotherapy and endocrine therapy which are discussed in section 2 of this article.

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